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Ultrasound Mediated, Sodium Bisulfite Catalyzed, Solvent Free Synthesis of 6-Amino-3-methyl-4-substitued-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile

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ABSTRACT. A simple, convenient and practical green synthetic protocol for sodium bisulfite catalyzed multicomponent reaction of ethyl acetoacetate, hydrazine hydrate, malononitrile, and various aldehydes for the synthesis of 6-amino-4-phenyl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles using ultrasound irradiations in solvent free condition. This method provides the advantage of operational simplicity, shorter reaction time and excellent yields making the protocol environment friendly and economically lucrative.

Key words: Pyrano[2,3-*c*]pyrazole, Substituted aldehydes, Sodium bisulfite catalyst

INTRODUCTION

The multi component reactions are emerging trend in the synthetic transformations due to its operational simplicity, occurring with less or minimum side products giving higher yields of the desired products. The advantage of the multi component reactions over the multi step reaction is simple experimental procedure, occurring in a single step giving higher yields from easily available starting materials without isolation of any intermediate, thus in turn, saving time, energy and raw materials required for the reaction making the protocol economically attractive and environment friendly.[1] Numbers of methods are being explored to develop a green chemistry protocol for the synthesis of biodiverse heterocycles by employing the multicomponent reaction in ultrasonicator.[1] In past decade, several methods have been developed using ultrasound irradiation as the unconventional source of energy, accelerating the synthetic reactions. Ultrasound irradiation being advantageous over the conventional thermal reactions as it reduces the time and increases the yield of product generally by minimizing the side products associated with the prolonged heating, and provide an convenient practical eco-friendly protocol for the reaction.[1] In recent years, pyrano[2,3-*c*]pyrazole molecule is a emerging class of heterocycles and is widely explored as it is an important core of the emerging drugs along with wide medicinal applications as, potential inhibitors of human Chk1 kinase,[2] antiinflammatory,[3] anticancer, analgesic,[3] molluscicidal activity,[4] and as antimicrobial.[5]

The synthesis of substituted Pyrano[2,3-*c*]pyrazole can be accomplished in several ways, like by the use of 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene in the presence of triethylamine.[6] Literature reveals methods employing, piperazine,[7] β-cyclodextrin,[8] γ-alumina as catalysts have been developed for the synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles. Even though, the reported methods are effective, they have their own limitation in terms of toxicity arising by the use of piperazine and piperidine.[6] Secondly, these methods employ expensive catalyst for the reaction.[8] In addition, solvent is required for the reaction,[7,8] making the work up procedure tedious and cumbersome.

The appealing biological application of the substituted pyrano[2,3-*c*]pyrazole molecule drive us to develop new methodology by minimizing or overcoming the drawbacks of the literature methods. In continuation of our research on development of new methodologies for synthesis of biologically important heterocycles keeping the eco-friendly approach in mind.[9] Herein, we wish to report the ultrasound assisted synthesis of substituted pyrano [2,3-*c*]pyrazole, by the simple, convenient and practical green synthesis protocol using sodium bisulfite as a catalyst. The key features of this methodology are operational simplicity, shorter reaction time and excellent yields making the protocol environment friendly and economically lucrative.

RESULTS AND DISCUSSION

Our continued interests for the development of efficient and environmentally friendly procedures for the synthesis of heterocyclic compounds, the catalytic activity of sodium bisulfite with its easy availability, cheap cost, and operational simplicity prompted us to explore the synthesis of substituted pyrano[2,3-*c*]pyrazole, in a one-pot reaction in the presence of sodium bisulfite which is being deeply studied as a catalyst over past decade by us.[9]

To screen the catalyst and to explore the effect of catalyst on reaction conditions, initially we examined catalyst free reaction condition product was formed but it took unusually longer reaction time and the yield was also not significant (*Table* 1), compared to the literature methods.[7,8] Encouraged with our initial observation, we tried to explore the catalytic activity of various catalysts like Et_3N, Et_2NH, K_2CO_3, pyridine, piperidine, dimethyl amino pyridine (DMAP), pyrrolidine, morpholine, L-proline and sodium bisulfite assisted by using ultrasound as mentioned in *Table* 1.

By evaluating the results obtained in *Table* 1 piperidine, DMAP, pyrrolidine, L-proline and sodium bisulfite showed promising results in terms of yields of reaction. The testing of the catalyst on this parameter of time reviled that DMAP, L-proline, and sodium bisulfite were the best of the lot in presence and absence of solvent (*Table* 1). In comparison with DMAP and L- proline the sodium bisulfite was found to be far superior for this reaction both in terms of the reaction time and yield.

To study the optimum catalytic loading for the reaction,

***Table* 1.** Optimization of catalyst for the synthesis of 6-amino-2,4-dihydro-3-methyl-4-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (5a)[a]

Sr. No.	Catalyst	Mol % of Catalyst	Solvent	Reaction Time in min	% Yield[b]
1	No Catalyst	0	Ethanol	60	75
2	Et_3N	50	Ethanol	5	80
3	Et_2NH	50	Ethanol	5	82
4	K_2CO_3	50	Ethanol	1	80
5	Pyridine	50	Ethanol	3	78
6	Piperidine	50	Ethanol	2	88
7	DMAP	50	Ethanol	1	90
8	DMAP	50	Solvent Free	45 sec	92
9	Pyrrolidine	50	Ethanol	2	82
10	Morpholine	50	Ethanol	5	75
11	L-Proline	50	Ethanol	1	92
12	L-Proline	50	Solvent Free	45 sec	94
13	Sodium bisulfite	50	Ethanol	1	97
14	Sodium bisulfite	50	Solvent Free	30 sec	99

[a]Reaction of ethyl acetoacetate (10 mmol), hydrazine hydrate (10 mmol), malononitrile (10 mmol), benzaldehyde (10 mmol), and catalysts under ultrasonic waves and solvent-free condition at 30 °C.
[b]Isolated yield.

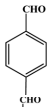
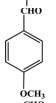
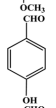
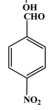
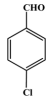
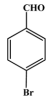
***Table* 2.** Optimization of catalyst loading for the synthesis of 6-amino-2,4-dihydro-3-methyl-4-phenylpyrano[2,3-*c*]pyrazole-5-carbonitrile (5a)[a]

Sr. no.	Mol % of catalyst	Solvent	Time in min	% Yield[b]
1	50	Water	3	88
2	50	Acetonitrile	5	75
3	50	Ethanol-Water	2	90
4	50	Ethanol	1	92
5	50	Solvent Free	30 sec	99
6	40	Solvent Free	30 sec	99
7	30	Solvent Free	30 sec	99
8	20	Solvent Free	30 sec	99
9	10	Solvent Free	30 sec	99
10	5	Solvent Free	45 sec	84

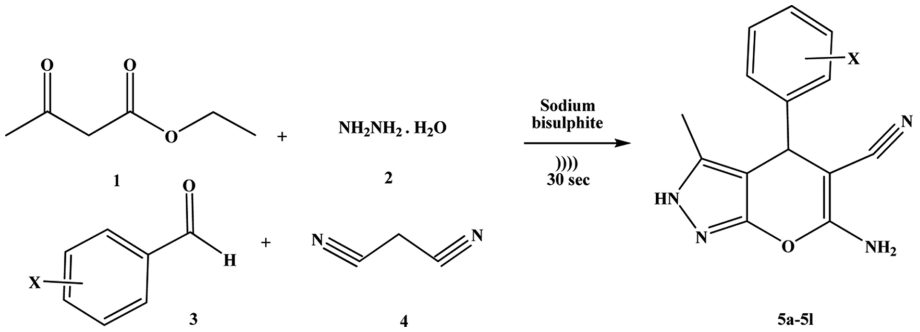
[a]Reaction of ethyl acetoacetate (10 mmol), hydrazine hydrate (10 mmol), malononitrile (10 mmol), benzaldehyde (10 mmol), and sodium bisulfite (0.10 mmol) under ultrasonic waves and solvent-free condition at 30 °C.
[b]Isolated yield.

sodium bisulfite was used in combination of various solvents like water, acetonitrile, ethanol-water, ethanol and in solvent free conditions. Surprisingly, it was observed that reaction proceeded smoothly in absence of solvent, which might be due to the ultrasonic cavitations creating microscopic internal high pressure and high temperature.[10] The results from *Table* 2 indicate that the reaction can proceed to completion without the use of solvent in shorter reaction time and better yield compared to the solvents enlisted above. The 10 mol% of sodium bisulfite was found to be ideal for the completion of the reaction in shorter reaction time and better yields; lower concentration of sodium bisulfite results in increase in reaction time and decrease in yield. Also, higher concentration of sodium bisulfite does not appreciably improve the yield and time of reaction. Thus, the 10 mol% of sodium bisulfite was sufficient for the reaction to go completion the developed method was economically lucrative. After optimizing the reaction conditions, the generality of this method was evaluated by using substituted aromatic aldehydes containing electron withdrawing and electron donating group and heterocyclic aldehydes to give the corresponding products as shown in *Table* 3 without any remarkable difference in yields and time of reaction.

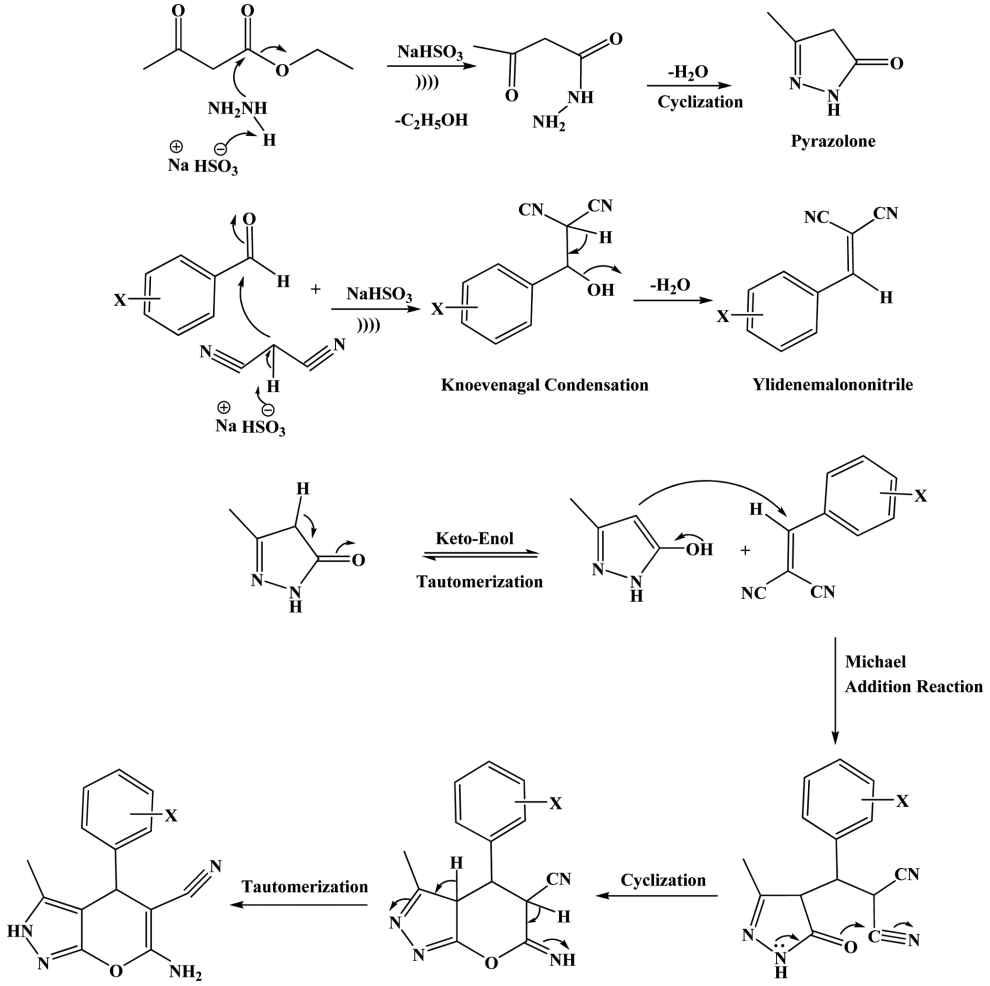
***Table* 3.** Synthesis of substituted pyrano[2,3-*c*]pyrazole catalyzed by sodium bisulfite under ultrasonic irradiation[a]

Sr. no.	Substituted Aldehyde	Time in sec	Melting point °C	Reference Melting point °C	% Yield[b]
5a		30	244-246	244-246[8]	99
5b		30	205-207	206-208[8]	99
5c		30	210-212	210-212[8]	99
5d		30	222-224	224-226[8]	99
5e		40	250-252	251-253[8]	97
5f		30	193-195	193-195[8]	98
5g		30	232-234	234-236[8]	98
5h		30	144-146	145-147[8]	98
5i		30	178-180	178-180[8]	99
5j		35	172-174	175-177[8]	
5k		40	187-189	190-191[8]	98
5l		40	215-217	218-219[8]	97

[a]Reaction of ethyl acetoacetate (10 mmol), hydrazine hydrate (10 mmol), malononitrile (10 mmol), substituted aldehydes (10 mmol), and sodium bisulfite (0.10 mmol) under ultrasonic waves and solvent-free condition at 30 °C.
[b]Isolated yield.
[c]All the melting point are uncorrected.
[d]All the compounds were characterised by IR, Mass and ^{1}H NMR and were compared with the reference compounds.



***Scheme* 1.** Synthesis of substituted pyrano[2,3-*c*]pyrazole catalyzed by sodium bisulfite under ultrasonic irradiation.



***Scheme* 2.** Plausible reaction mechanism for the synthesis of substituted pyrano[2,3-c]pyrazole catalyzed by sodium bisulfite under ultrasonic irradiation.

Herein, we propose a possible mechanism for the synthesis of pyrano[2,3-*c*]pyrazole, in a one-pot reaction in the presence of sodium bisulfite. Firstly, there is Knoevenagel condensation between the aldehyde and the malononitrile leading to formation of the ylidenemalononitrile by the loss of water molecule. Simultaneously the reaction occurring between the hydrazine hydrate and ethyl acetoacetate yields pyrazolone by with the elimination of ethanol and water molecule. This ylidenemalononitrile and pyrazolone undergoes the Michael addition reaction followed by the ring closure and the tautomerization to give the pyrano[2,3-*c*]pyrazole as the product.

The advantage of this method over the reported method[7,8] is easily available and cheap catalyst, operational simplicity. Also, the time required for the completion of reaction is less (30 sec) as compared to that of the literature method[8] which requires more than 50-70 min for its completion and the yields ranging from 80-90%. In summary, we have developed an efficient environment friendly, economically lucrative and practical method for the synthesis of substituted pyrano[2,3-*c*]pyrazole in shorter reaction time and excellent yields.

CONCLUSION

In conclusion, we have developed a highly efficient environment friendly, economically lucrative, convenient and practical method for ultrasound assisted one-pot method for the synthesis of substituted pyrano[2,3-*c*]pyrazole catalyzed by sodium bisulfite. The developed method is simple, robust and practical, which proceeds without any special handling technique and requiring routine reagents. Thus, this one-pot green chemistry protocol is advantageous requiring lesser reaction time, operational simplicity with ease of execution to give high yields.

EXPERIMENTAL

The ethyl acetoacetate, hydrazine hydrate, malononitrile, substituted aldehydes, and sodium bisulfite were commercially available. Melting points were recorded on SRS Optimelt melting point apparatus and are uncorrected. IR spectra were recorded using BRUCKER FT-IR 4000 in KBr powder. Ultrasonication was performed in an Ultrasonic Bath Sonicator of PCI Analytics,® having ultrasound cleaner with a frequency of 35 kHz and an nominal power of 200 W. The reaction flask was located in close proximity of the maximum energy area in the cleaner such that the reaction vessel was slightly lower than the water level and the temperature of the water bath was controlled at 30 °C. ^{1}H NMR spectra were recorded on a 400 MHz Varian-Gemini spectrometer and are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplate (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

General Procedure for the Synthesis of Substituted Pyrano[2,3-c]pyrazole

In a RBF ethyl acetoacetate (10 mmol), hydrazine hydrate (10 mmol), malononitrile (10 mmol), substituted aldehydes (10 mmol), and sodium bisulfite (0.10 mmol) were charged. The mixture was irradiated using ultrasound radiation for 30 sec at 30 °C and the progress of the reaction was monitored till completion on TLC (ethyl acetate: n-hexane 1:4).The solid obtained was filtered and washed with water (2×5 ml). The crude product was recrystallized by using ethanol. The pure products were collected in 97-99% yields.

Spectral Characterization of Representative Compounds

6-amino-2,4-dihydro-3-methyl-4-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (5a):

Yellow solid, IR (KBr): cm^{-1}, 870, 1260, 1380, 1590, 1625, 2915, 3060, 3410; ES-MS *m/z* (%): 253 (M+H), ^{1}H NMR (400 MHz, $CDCl_3$) 1.87 (s, 3H); 4.90 (s, 1H); 6.75 (s br, 2H); 7.10-7.65 (m, 5H); 12.35 (s, 1H).

6-amino-4-(4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5d):

Off white solid, IR (KBr): cm^{-1}, 878, 1271, 1368, 1583, 1645, 2922, 3056, 3350, 3410; ES-MS *m/z* (%): 269 (M+H), ^{1}H NMR (400 MHz, $CDCl_3$) 1.91 (s, 3H); 4.97 (s, 1H); 5.67 (s, 1H) 6.82 (s br, 2H); 7.18-7.69 (m, 4H); 12.15 (s, 1H).

6-amino-3-methyl-4-(3-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5f):

Yellow solid, IR (KBr): cm^{-1}, 876, 1255, 1371, 1582, 1620, 2925, 3045, 3425, ES-MS *m/z* (%): 298 (M+H), ^{1}H NMR (400 MHz, $CDCl_3$) 1.94 (s, 3H); 5.12 (s, 1H); 6.94 (s br, 2H); 7.14-7.81 (m, 4H); 12.40 (s, 1H).

6-amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5g):

White solid, IR (KBr): cm^{-1}, 879, 1255, 1372, 1581, 1627, 2929, 3025, 3425, ES-MS *m/z* (%): 287(M+H), ^{1}H NMR (400 MHz, $CDCl_3$) 1.91 (s, 3H); 5.18 (s, 1H); 6.91 (s br, 2H); 7.11-7.80 (m, 4H); 12.44 (s, 1H).

6-amino-3-methyl-4-(pyridin-4-yl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5l):

Yellow solid, IR (KBr): cm^{-1}, 870, 1260, 1380, 1590, 1625, 2915, 3062, 3415; ES-MS *m/z* (%): 254 (M+H), ^{1}H NMR (400 MHz, $CDCl_3$) 1.92 (s, 3H); 4.98 (s, 1H); 6.68 (s br, 2H); 7.14-7.86 (m, 4H); 12.36 (s, 1H).

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